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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/418,095	10/14/1999	JOHN A. COPLAND III	UTMB/GAL:239	8391

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	11

DATE MAILED: 07/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Applicati n N .	Applicant(s)	
	09/418,095	COPLAND III ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed April 11, 2002 is acknowledged.

Examiner noted that amended claims 5-6 do not match with the marked up claims 5-6. However, for the purpose of a compact prosecution Applicants' amendment has been entered as Paper No. 9.

Claims 1-46 are pending in the present application.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Claim Objections

Claim 18 is objected to because of the following informalities: the term "alklyating" is misspelled. Appropriate correction is required.

Specification

In the Brief Description of the Drawings sections, on page 15, Applicants describe Fig. 17 and Fig. 18. However, there are Fig. 17A-C and Fig. 18A-B in the present application. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claim 32 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to

make and/or use the invention for the same reasons set forth in the previous Office Action.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The claim is directed to a method for inhibiting the growth of a cancer cell comprising (i) contacting the cancer cell with a thiazolidinedione compound; and (ii) contacting the cancer cell with a chemotherapeutic drug or irradiating the cancer cell with X-ray irradiation, UV-irradiation, γ-irradiation, or microwaves, in amounts effective to inhibit the growth of the cancer cell, wherein the thiazolidinedione compound is contacted with a cancer cell by administering the thiazolidinedione regionally, endoscopically, intravenously, intralesionally, percutaneously, subcutaneously, intraperitoneally, intratracheally, intramuscularly, or by perfusion, and wherein further comprising contacting the cell with a therapeutic polynucleotide selected from the group consisisting of a Dp gene, p21, p16, p27, E2F, Rb, APC, DC, NF-1, WT-1, MEN-1, MEN-11, BRCA1, VHL, FCC, MCC, ras, myc, neu, raf, erb, src, fms, jun, trk, ret, gsp, hst, bcl, abl, Bax, Bcl-Xs and E1A, wherein the therapeutic polynucleotide is expressed in the cell.

The specification teaches a method utilizing troglitazone or other thiazolidinedione compounds such as pioglitazone, rosiglitazone either alone or in combination with other chemotherapeutic agents known in the art to treat cancer. Specifically, the specification discloses that osteosarcoma Saos-2 cells contain functional PPAR-gamma and upon exposing the cells to troglitazone, osteosarcoma cell proliferation measured by total DNA content and thymidine incorporation is inhibited. The specification further teaches that troglitazone is effective in lowering the doses of 5-fluorouracil (5-FU) and doxorubicin required for inhibiting the proliferation of Saos-2 cells. Among the thiazolidinedione compounds tested in this cell culture system, troglitazone is shown to be superior to pioglitazone and rosiglitazone (BRL 49653) in its ability to inhibit cell proliferation. Similar inhibition effects of troglitazone, pioglitazone and rosiglitazone on cell proliferation of human renal URMC 3, 6 and 7 tumor cells were observed. Various human ovarian cancer cell lines including CaOV3, 222, PA-1, 2774, OV CAR3 and SK OV3 were also tested for the proliferation inhibitory effects of the thiazolinedione compounds. The data suggested that responsiveness of individual thiazolidinedione could not be predicted in these ovarian cell lines. Furthermore, in a combined application of taxol and troglitazone to isolated human ovarian tumor cells, an enhanced inhibitory activity over that of either agent used alone was obtained, however this enhanced inhibitory effect is significantly less than that obtained for the commonly used regimen of taxol and cisplastin already known in the art.

The above evidence has been noted and considered. However, it is not reasonably extrapolated to the instant claimed invention. The nature of claim 32 would

fall within the realm of *in vivo* gene therapy. At the effective filing date of the present application, the art of gene therapy was highly unpredictable regarding to obtaining desired therapeutic effects. In a meeting report on gene therapy and translational cancer research, Dang et al. (Clin. Cancer Res. 5:471-474, 1999; Cited previously) stated that "This workshop reviewed some recent advances in gene delivery, gene expression, immune manipulation, and the development of molecular targets and stressed that all of these fields will need further advancement to make gene therapy a reality" (page 471, col. 1, last sentence of first full paragraph). There are several factors known to limit the effectiveness of gene therapy, these include, the lack of optimal vectors, the lack of stable *in vivo* transgene expression, the adverse host immune responses to the vectors, and most importantly the lack of an efficient gene delivery to target tissues (page 474, col. 2, last paragraph). The instant specification fails to provide any relevant information regarding to the specific vectors used, the effective dosage of the vectors utilized, the route and frequency of administering these vectors to cancer cells such that effective amounts of encoded polypeptides listed in the claim could be expressed to yield the desired therapeutic effects. There is no evidence of record indicating or suggesting any of the recited therapeutic polynucleotide could be expressed at an effective amount in cancer cells to yield any therapeutic effects, let alone any additional or synergistic therapeutic effects to be attained in combination with a thiazolidinedione compound and a chemotherapeutic drug or irradiation. Particularly, for inhibiting the growth of a variety of cancer cell types contemplated by Applicants. The CAFC has stated "patent protection is granted in return for an enabling disclosure,

not for vague intimations of general ideas that may or may be workable". The court also stated that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genetech, Inc. v. Novo Nordisk A/S*, 42 USPQ 2d 1001, at 1005).

Regarding to the breadth of the instant claim encompassing a laundry list of therapeutic polynucleotides, it should be noted that additional factors such as the level of mRNA produced, the stability of the protein produced, the protein's proper compartmentalization within the cell differ dramatically based on which protein being produced, and therefore the desirable therapeutic effects sought to achieve (Eck & Wilson, Gene-based therapy, 1996, column 2 page 81 continues to page 82; Cited previously). With the level of transgene expression, its duration, and its *in vivo* therapeutic effects are not predictable, coupled with the lack of guidance provided by the present disclosure, it would have required undue experimentation for one skilled in the art to make and use the claimed invention.

The instant claim also encompasses any route of administering a therapeutic polynucleotide *in vivo* to contact the cancer cell. Vector targeting *in vivo* to desired cells or organs continues to be unpredictable and inefficient. This is supported by numerous teachings in the art. For example, Miller & Vile (FASEB 9:190-199, 1995; Cited previously) reviewed the types of vectors available for *in vivo* gene therapy, and concluded that "Targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly

efficient delivery systems" (page 198, column 1). Deonarain (Exp. Opin. Ther. Patents 8:53-69, 1998; Cited previously) indicated that one of the main obstacles hampering a successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time." (page 53, first paragraph). Deonarain also reviewed new techniques under experimentation in the art which show promises. One of which is the ligand-targeted receptor-mediated vector approach with a relatively higher level of tissue specificity than viruses can offer. However, this approach to gene therapy is much less efficient than viral gene delivery (column 1, last paragraph, page 65). Verma & Somia (Nature 389:239-242,1997; Cited previously) reviewed various vectors known in the art for use in gene therapy, and the problems which are associated with each. They also indicated clearly that resolution to vector targeting had not been achieved in the art at about the effective filing date of the present application (see the entire article). Verma & Somia discussed the role of the immune system in inhibiting the efficient targeting of viral vectors such that an efficient expression is not achieved (see page 239, and second and third columns of page 242). Verma & Somia also indicated that appropriate enhancer-promoter sequences can improve expression, but that the "search for such combinations is a case of trial and error for a given cell type." (page 240, sentence bridging columns 2 and 3). The instant specification fails to teach one of skill in the art how to overcome the unpredictability for *in vivo* vector targeting such that an efficient transfer and expression of a recited therapeutic polynucleotide could be achieved by any mode of gene delivery to yield the therapeutic effects contemplated by Applicants.

Accordingly, due to the lack of guidance provided by the instant specification regarding to the issues set forth above, the unpredictability of the gene therapy art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instantly claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on April 11, 2002 in Paper No. 10 (pages 4-7) have been fully considered.

Applicants argued that methods of contacting a cell with a polynucleotide such that the polynucleotide is expressed in the cell were well known in the art at the time of the present invention, including the references cited by Examiner showing various methods of delivering therapeutic polynucleotides to cells as well as numerous viral and non-viral DNA delivery strategies. Additionally, proof of efficacy in clinical trials involving humans is not a requirement for patentability. With respect to Dang reference, Applicants argued that Dang focuses on more clinical issues that are above and beyond the standards of patentability. Similarly, Eck reference addresses the clinical effectiveness of gene therapy as a whole. Applicants further argued that the duration of expression of the transgene in cancer therapy is less of an issue than it is for inherited disorders. Moreover, Applicants contend that the level of skill in the art at the time of the present invention was such that the guidance provided in the present disclosure would enable one skilled in the art to make and use the claimed invention.

Applicants' arguments are found unpersuasive because while Examiner acknowledges that proof of efficacy in clinical trials involving humans is not a requirement for patentability, the instant specification fails to provide sufficient guidance for a skilled artisan to make and use the method as claimed. Although gene therapy trials have been conducted and methods of delivering polynucleotides to cells have been described, it is the attainment of therapeutic effects through gene therapy that remains unpredictable because of the various unpredictable factors involved in determining the effective expression level of a therapeutic transgene in a desired cell to yield the contemplated results. These unpredictable factors as well as the immature state of gene therapy art at the effective filing date of the present application have been discussed in the cited references above. The present disclosure fails to provide any specific guidance (e.g., specific vectors used, the effective dosage of the vectors utilized, the route and frequency of administering these vectors to cancer cells) for a skilled artisan on how to obtain an effective expression level of any gene selected from a long laundry list comprising Dp gene, p21, p16, p27, E2F, Rb, APC, DC, NF-1, NF-2, WT-1, MEN-I, MEN-II, BRCA1, VHL, FCC, MCC, *ras*, *myc* and others in cancer cells to yield any therapeutic effects (e.g., inhibiting the growth of cancer cells) contemplated by Applicants. Nor does the present disclosure provide any reasonable correlated *in vivo* example (part of guidance), particularly in light of the unpredictability of the gene therapy art for obtaining therapeutic effects. Therefore, it would have required undue experimentation for a skilled artisan to make and use the instant claimed invention. Furthermore, Applicants' arguments fail to provide any factual evidence indicating that

at the effective filing date of the present application, *in vivo* vector targeting has been overcome as the references cited by Examiner clearly indicate that this is a major hurdle or challenge that limits the attainment of therapeutic effects via gene therapy by any route of delivery.

Accordingly, claim 32 remains rejected under 35 U.S.C. 112, first paragraph for the reasons stated above. Additionally, Examiner would like to note that claims 1 and 25 from which claim 32 is dependent upon, also contain an embodiment of claim 32 would be rejected for the same reasons.

Claim Rejections - 35 USC § 102

Claims 1-8, 16, 28, 33-35 and 40-41 remain rejected under 35 U.S.C. 102(e) as being anticipated by Urban et al. (U.S. Patent No. 5,814,647 with the effective filing date of 3/4/1997) as evidenced by Medenica et al. (U.S. Patent No. 5,736,129), Knight et al. (U.S. Patent No. 6,090,407) and Roth et al. (U.S. Patent No. 5,747,469) for the same reasons set forth in the previous Office Action in Paper No. 9.

Urban et al. teach that troglitazone and related thiazolidinedione compounds (including pioglitazone and BRL49653, see example 1) can be used in the treatment of the climacteric and cancer. Specifically, Urban et al. disclose that therapeutic levels of troglitazone can kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-9). A type of cancer that is likely to be treated with troglitazone and related thiazolidinedione derivatives are mesenchymal tumors including but not limited to sarcomas, congenital

mesoblastic nephroma, rhabdomyosarcomas, fibrosarcomas, hemangiopericytoma and mesotheliomas (col. 3, lines 13-22). Urban et al. also stated "Use of troglitazone therapy in conjunction with other chemotherapeutic agents, radiation, or surgery may in many cases be the preferred mode of treatment. Troglitazone treatment therefore, would inhibit the growth of the cancer so that other therapies may be added, thereby increasing the likelihood of curing the patient. Troglitazone and related thiazolidinedione derivatives may additionally be used to treat patients with severely metastatic disease. Such treatment may slow tumor growth and reduce tumor mass, thereby prolonging survival and increasing the quality of terminal cancer patients" (col. 24, lines 17-27). Although Urban et al. do not teach specifically the types of chemotherapeutic drugs utilized or types of radiation used in combination with the troglitazone therapy, however the types of chemotherapeutic drugs and the types of radiation utilized in the treatment of cancer are well known in the art as evidenced by the teachings of Medicina et al., Knight et al., and Roth et al. Medenica et al. disclosed treating cancer cells by the use a multidrug chemotherapeutic regiment. The utilized drugs that are taught in the issued patent encompass alkylating agents such as Cis-platin, cyclophosphamide; mitotic inhibitors such as etoposide or VP-16, taxol, vinblastine; antibiotics such as doxorubicin, dactinomycin; an antimetabolite such as 5-FU and a corticosteroid hormone such as prednisone (See columns 6-10). Knight et al. teach the use of anti-cancer drugs including a nitrosourea agent such as lomustine, and others such as taxol, 5-FU, etoposide... for treating cancer (See claim 1 on column 16). Roth et al. teach killing cancerous cells using a tumor suppressor gene, p53 in a

recombinant retrovirus, in combination with a DNA damaging agent. An embodiment of the invention disclosed by Roth et al. involves the use of gamma-irradiation, X-rays, UV-irradiation or microwaves as a DNA damaging agent in combination with p53 gene transfer to treat cancer (column 8, second paragraph and see claims 51 and 61-67). Roth et al. further noted that a combination treatment is required to prevent local recurrence following primary tumor resection (See column 3, lines 20-25).

Accordingly, Urban et al. anticipate the instant claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on April 11, 2002 in Paper No. 10 (pages 7-8) have been fully considered.

Applicants argued "Prior to the Applicants' disclosure it was not known whether the use of thiazolidinedione therapy in combination with other chemotherapeutic agents or radiation would inhibit the growth of a cancer cell". Additionally, Applicants argued "The disclosure of Urban of the use of troglitzone in combination with chemotherapeutic drugs or radiation was not based on actual experiments; it was merely a prophetic example. Due to the lack of predictability in the art, such a disclosure would not enable one of ordinary skill in the art to make and use the invention". Applicants' arguments are respectfully found unpersuasive for the following reasons.

Firstly, Urban et al. clearly teach the essential concept of using troglitazone (as well as related thiazolidinedione compounds such as pioglitazone and BRL49653)

therapy in conjunction with other chemotherapeutic agents, radiation, or surgery for the treatment of cancer. Therefore, Urban et al. anticipate the instant claimed invention.

Secondly, with respect to Applicants' argument of the unpredictability of the art, it is unclear which unpredictable factors are involved in cancer treatment or killing cancer cells via the combined uses of troglitazone or related thiazolidinedione compounds with other chemotherapeutic agents, radiation or surgery. Chemotherapeutic agents, radiation or surgery are routinely used in cancer treatment at the effective filing date of the present application as evidenced by the teachings of Medenica et al., Knight et al. and Roth et al. as discussed above. In addition to the teachings of Urban et al. on the use of troglitazone and related thiazolidinedione compounds to kill transformed cell lines and human breast cancer MCF-7 cell line (see examples 5 & 6), at the effective filing date of the present application Mueller et al. (Mol. Cell 1:465-470, 1998; Cited previously) demonstrated that troglitazone or pioglitazone decreases the growth of human breast cancer 21PT cells; Brockman et al. (Gastroenterology 115:1049-1055, 1998; Cited previously) showed that BRL 49653 or rosiglitazone inhibits the growth of human colon cancer cells derived from various cell lines HCA-7, HCT-116, HCT-15 and HCT-15-G25; Elstner et al. (Proc. Natl. Acad. Sci. USA 95:8806-8811, 1998; Cited previously) disclosed clonal proliferation of human breast cancer cells derived from cell lines MCF7, T47D, MDA-MB-231 were inhibited by troglitazone (TGZ) in a concentration-dependent manner, and that this inhibition was further enhanced with the combination of TGZ and all-*trans*-retinoic acid (ATRA) which is an antineoplastic chemotherapeutic agent; Kubota et al. (Cancer Res. 58:3344-3352, 1998; Cited

previously) taught that troglitazone and other PPAR-gamma ligands including BRL49653 and others have anti-proliferative effects on the human PC-3 prostate cancer cells; and Tontonoz et al. (Proc. Natl. Acad. Sci. 94:237-241, 1997; IDS) disclosed that thiazolidinedione compound such as pioglitazone, troglitazone and BRL49653 (rosiglitazone) can induce terminal differentiation of human liposarcoma cells *in vitro*, and that thiazolidinedione-induced differentiation of liposarcoma cells is accompanied by cell cycle growth arrest, which is in effect inhibiting liposarcoma cell growth. Moreover, Examiner also would like to direct Applicants to the claims of U.S. Patent No. 6,207,690 issued to Urban et al., which are directed to methods of treating a tumor in a subject using troglitazone, pioglitazone and BRL 49653. This patent claims priority to the cited U.S. Patent No. 5,814,647, indicating that the disclosure of U.S. Patent No. 5,814,647 is enabled for the use of a thiazolidinedione compound for treating cancer. Therefore, it is unclear what exactly is not predictable regarding to the combined uses of troglitazone or related thiazolidinedione compounds with other chemotherapeutic agents, radiation or surgery for treating or killing cancer cells? Applicants have failed to provide any factual evidence or reasonable scientific reasoning what or why the art is unpredictable from the combined uses of troglitazone or related thiazolidinedione compounds with other chemotherapeutic agents, radiation or surgery for treating or killing cancer cells, particularly when taken the state of the relevant art as a whole at the effective filing date of the present application as discussed above.

Thirdly, Examiner noted that Applicants solely disclosed the growth inhibitory effects of troglitazone, pioglitazone or BRL49653 alone or in combination with

chemotherapeutic agents on cultured osteosarcoma cells, cultured human renal tumor cells and cultured human ovarian cancer cells. With the respect to Applicants' argument on the unpredictability of the art, do Applicants really question the enablement of their own claims directed to *in vivo* methods, particularly for those recite therapeutic effects?

Accordingly, claims 1-8, 16, 28, 33-35 and 40-41 remain rejected for the reasons set forth above.

Claim Rejections - 35 USC § 103

Claims 1-31 and 33-46 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tontonoz et al. (Proc. Natl. Acad. Sci. 94:237-241, 1997; IDS) in view of Urban et al. (U.S. Patent No. 5,814,647 with the effective filing date of 3/4/1997), Medenica et al. (U.S. Patent No. 5,736,129), Knight et al. (U.S. Patent No. 6,090,407) and Roth et al. (U.S. Patent No. 5,747,469) for the same reasons set forth in the previous Office Action in Paper No. 9.

Tontonoz et al. disclose that thiazolidinedione compound such as pioglitazone, troglitazone and BRL49653 (rosiglitazone) can induce terminal differentiation of human liposarcoma cells *in vitro*, and that thiazolidinedione-induced differentiation of liposarcoma cells is accompanied by cell cycle growth arrest, which is in effect inhibiting liposarcoma cell growth (see the entire article, particularly page 240, col. 1). Tontonoz et al. further teach that thiazolidinedione compounds, at least for pioglitazone and BRL49653, have additive effects on terminal differentiation of human liposarcoma cells

with an RXR-specific ligand LG268. Moreover, on the basis of their data, Tontonoz et al. suggested that thiazolidinedione compounds and RXR-specific retinoids can be used to stimulate differentiation and growth arrest of human tumors *in vivo* (page 241, col. 1, second full paragraph). Tontonoz et al. do not teach contacting the cancer cells with a chemotherapeutic drug or irradiating the cancer cell with X-ray irradiation, UV-irradiation, γ-irradiation or microwaves in combination with a thiazolidinedione compound, or specific cancer cell types recited in dependent claims or specific steps in certain methods claimed.

Urban et al. teach that troglitazone and related thiazolidinedione compounds can be used in the treatment of the climacteric and cancer. Specifically, Urban et al. disclose that therapeutic levels of troglitazone can kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-9). A type of cancer that is likely to be treated with troglitazone and related thiazolidinedione derivatives are mesenchymal tumors including but not limited to sarcomas, congenital mesoblastic nephroma, rhabdomyosarcomas, fibrosarcomas, hemangiopericytoma and mesotheliomas (col. 3, lines 13-22). Urban et al. also stated "Use of troglitazone therapy in conjunction with other chemotherapeutic agents, radiation, or surgery may in many cases be the preferred mode of treatment. Troglitazone treatment therefore, would inhibit the growth of the cancer so that other therapies may be added, thereby increasing the likelihood of curing the patient. Troglitazone and related thiazolidinedione derivatives may additionally be used to treat patients with severely metastatic disease. Such treatment may slow tumor growth and

reduce tumor mass, thereby prolonging survival and increasing the quality of terminal cancer patients" (col. 24, lines 17-27).

Medenica et al. disclosed a method of treating cancer cells by the use a multidrug chemotherapeutic regiment. The utilized drugs that are taught in the issued patent encompass alkylating agents such as Cis-platin, cyclophosphamide; mitotic inhibitors such as etoposide or VP-16, taxol, vinblastine; antibiotics such as doxorubicin, dactinomycin; an antimetabolite such as 5-FU and a corticosteroid hormone such as prednisone (See columns 6-10). Knight et al. taught a method of delivering anti-cancer drugs including a nitrosourea agent such as lomustine, and others such as taxol, 5-FU, etoposide... in treating cancer (See claim 1 on column 16). Roth et al. disclosed a method of killing cancerous cells using a tumor suppressor gene, p53 in a recombinant retrovirus, in combination with a DNA damaging agent. An embodiment of the invention disclosed by Roth et al. involves the use of gamma-irradiation, X-rays, UV-irradiation or microwaves as a DNA damaging agent in combination with p53 gene transfer to treat cancer (column 8, second paragraph and see claims 51 and 61-67). Roth et al. further noted that a combination treatment is required to prevent local recurrence following primary tumor resection (See column 3, lines 20-25).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify a method disclosed by Tontonoz et al. by combining the use of a thiazolidinedione compound (e.g., troglitazone, pioglitazone and rosiglitazone) in conjunction with other chemotherapeutic agents, radiation, or surgery to inhibit the growth or killing liposarcoma cells or mesenchymal tumor cells or tumor

cells expressing PPARγ in both *in vitro* and *in vivo* as taught by Urban et al. With respect to the effectiveness of thiazolidinedione in inhibiting the growth of a wide range of tumor cells, in the absence of the evidence to the contrary, the growth of recited tumor or cancer cells is also inhibited by thiazolidinedione. Therefore, it would have been obvious for one of ordinary skill to test the growth inhibitory effects of a thiazolidinedione compound to any known cancer cell lines or any cancer tissues and the use of a thiazolidinedione as an anti-cancer therapy in conjunction with other chemotherapeutic agents, radiation, or surgery. It is noted that although specific chemotherapeutic drugs and/or specific method steps involved in the combined therapies (thiazolidinedione with either chemotherapy or irradiation or surgery) are not taught in both Tontonoz et al. and Urban et al., at the effective filing date of the present application it is within the scope of skill of an ordinary skilled artisan to modify and carry out such recited limitations because the art on chemotherapy, irradiation and surgery for treating cancer is well known. This is exemplified by the teachings of Medenica et al., Knight et al., and Roth et al. as presented above. One of ordinary skill would have been motivated to carry out the above modification because it is apparent that a thiazoldinedione compound is useful in adjuvant therapy for cancer treatment due to its antiproliferative effects and its low toxicity and well tolerance in humans (thiazoldidinedione compounds are well known anti-diabetic drugs). Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

R sponse to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on April 11, 2002 in Paper No. 10 (pages 8-10) have been fully considered.

Applicants mainly argued that Tontonoz reference teaches away from combining thiazolidinedione therapy with chemotherapeutic drugs or radiation by recommending the use of thiazolidinedione compounds as an alternative to conventional chemotherapy (Tontonoz, p. 241, second full paragraph), and that the Urban reference is not enabled because the teachings are not based on actual experiments and due to the unpredictability in the art. Therefore, the claims are not obvious in light of the combined teachings of Tontonoz et al., Urban et al., Medenica et al., Knight et al. and Roth et al. Applicants' arguments are found unpersuasive for the following reasons.

Firstly, Tontonoz et al. simply stated "Our results suggest that the thiazolidinedione class of antidiabetic drugs and RXR-specific retinoids may be useful as a nontoxic alternative to conventional chemotherapy for the treatment of disseminated or locally advanced liposarcoma" (p. 241, second full paragragh). Nowhere in the Tontonoz reference that one can find teachings suggesting that thiazolidinedione compounds should not be used in conjuction with chemotherapeutic agents, radiation, or surgery for the treatment of cancers. Applicants are invited to point out the specific page numbers and the line numbers where such specific teachings are found in the Tontonoz reference. In the absence of such teaching, Tontonoz et al. do not teach away from combining thiazolidinedione therapy with chemotherapeutic drugs or radiation or surgery.

Secondly, this is a 103 rejection. Therefore, in light of the teachings of Urban et al., one of ordinary skilled artisan would be able to think and be motivated to combine the use of thiazolidinedione compounds in conjunction with chemotherapeutic drugs, radiation or surgery as clearly taught by Urban et al. Moreover, one of ordinary skill artisan would have been motivated to carry out the above modification because when taken the art of using a thiazolidinedione compound for cancer treatment as a whole at the effective filing date of the present application, it is readily apparent that a thiazoldinedione compound is useful in adjuvant cancer therapy due to its antiproliferative effects and its low toxicity and well tolerance in humans (thiazoldidinedione compounds are well known anti-diabetic drugs).

Thirdly, with respect to Applicants' arguments on the non-enabled disclosure of Urban et al. reference and the unpredictability of the art, they are found to be unpersuasive for the reasons already discussed in the Response to Arguments related to the rejection of claims 1-8, 16-23, 28, 30, 33-35 and 40-41 above.

Accordingly, claims 1-31 and 33-46 remain rejected for the reasons discussed above.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER